Is microalbuminuria progressive?

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Abstract
In 1990, 81 children and adolescents with insulin dependent diabetes were studied for early signs of diabetic nephropathy. Nine patients were identified as having microalbuminuria (incipient nephropathy). These subjects were re-examined three years later. In five of these cases, the second examination revealed normal albumin excretion; in three of the four cases in whom microalbuminuria persisted, the rate of albumin excretion had decreased. The general improvement in albumin excretion rates in the initially microalbuminuric group could not be explained by improved glycaemic control nor interventional drug treatment. The lack of progression in this microalbuminuric group from the original prevalence study suggests that this method of identifying early nephropathy in childhood may not be valid or that the progression of incipient nephropathy in childhood is more irregular or slower than in later life.
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The original work defining microalbuminuria as predictive of later onset overt nephropathy in at least 80% of cases was conducted in adults some 15 years ago.[1-3] In these studies various lower level cut off points for defining microalbuminuria were used varying from 15 to 70 µg/min. Microalbuminuria is now more generally defined as a timed urinary albumin excretion of between 20 and 200 µg/min.[4] A number of studies in childhood and adolescence have indicated a prevalence of between 5 and 15% for microalbuminuria assuming that the progression of disease is similar to that in adults.[5-7] However, follow up investigations in these studies have not been reported. We report the non-progression of microalbuminuria over a three year period in childhood and adolescence and question the applicability to children of work on adults with microalbuminuria.

Patients and methods
Eighty one children and adolescents (33 males, 48 females) seen at diabetes clinics in Bristol and examined in 1990 (D_1) were recalled for further examination in 1993/4. They were part of a prospective cohort study initiated in 1986 to examine various manifestations of childhood, subclinical microvascular disease.[8] At D_1, these 81 patients had been asked to collect two consecutive, timed, overnight urine collections. Having excluded urinary tract infection, these samples were analysed for albumin excretion rate (AER) with a median (mean) urinary AER $\geqslant 20$ and $\leqslant 200$ µg/min defining microalbuminuria.

In 1993/4 these patients were re-examined (D_2). On the three nights before the clinic visit they were given detailed instructions for collecting three, timed, overnight urine samples. None of these samples was collected at the time of menses. All samples were checked for infection before analysis. They were then kept at 4°C if there was to be any delay in protein estimation (maximum of three days).

Urinary albumin concentration was analysed by immunoturbidimetry at both D_1 and D_2 (Cobas Mira, Roche) allowing an excretion rate to be estimated using the total volume of urine passed and the timing of each collection. The coefficient of variation of the immunoturbidimetric analysis was 2·0–4·1% and the interassay variation 4·2%. Microalbuminuria was defined as a median albumin excretion rate between 20 and 200 µg/min.[4] Glycated haemoglobin was analysed on all patients using the Corning electroendosmosis technique throughout the study period. Urine creatinine was measured using a modification of the Jaffé method.

STATISTICAL METHODS
Two sample Student's *t* tests were used to compare mean glycated haemoglobin concentrations, after prior $\log_{10}$ transformation to remove skewness. A Wilcoxon matched pair signed ranks test was used to compare albumin excretion rates between D_1 and D_2. A Mann-Whitney U test was used to compare the ages of those with and without microalbuminuria.

Results
Seventy five (93%) of the original 81 patients returned for further examination. The six (five female, one male) who did not reattend were of a slightly older age, median 20·9 years (range 14·4–22·8) compared with those remaining, median 18·6 years (range 10·6–23·5). Five patients had moved out of the area and one declined repeated appointments. However, the local non-attender was able to provide a random urine collection for an albumin/creatinine ratio, 0·9 mg/mmol, making it extremely unlikely that a timed collection would have revealed microalbuminuria.[4]

For the remaining 75 patients the median age at D_1 was 15·7 years (range 7·4–21·0) and at D_2 18·6 years (10·6–23·5). There were 32 males and 43 females. The median time interval between D_1 and D_2 was 2·8 years (range

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2·3–3·7). Sixty five patients supplied three, six supplied two, and four supplied one overnight urine collection for analysis. In those four only supplying one overnight specimen (none of whom had microalbuminuria at D_1), an additional random urine specimen was taken at the clinic visit and assessed for an albumin/creatinine ratio. In all patients both the single overnight specimen and this random collection indicated normal albumin excretion (all random albumin/creatinine ratios <1 mg/mmol with the laboratory reference range for normality being <1·5 mg/mmol). At D_1 there were nine (five females, four males) and at D_2, seven patients with microalbuminuria (four females, three males). Only four of those who were microalbuminuric at D_1 remained so at D_2 and three new cases were identified as abnormal (figure). In the four cases remaining microalbuminuric, only one had a higher median AER at D_2 than at D_1 (table). In the study group as a whole, there was no significant trend in AER values between D_1 and D_2, the estimated intrapatient coefficient of variation for those with an average AER of 10 μg/min or greater was 83%. At D_1, those cases with microalbuminuria were significantly older than those with normal albumin excretion (median 18·5 years *v* 15·1 years; p=0·005).

Analysis of glycated haemoglobin from 1982 (or the time of diagnosis if later) before D_1 revealed a significantly higher level in those with either persistent or intermittent microalbuminuria compared with those with normal albumin excretion (geometric mean 12·5% (range 9·8–17·2%) *v* 10·6% (range 6·8–15·2%); p=0·001). In the subgroup of patients with microalbuminuria at D_1 there was no significant difference in glycated haemoglobin in the interim period between those remaining microalbuminuric and those reverting to normal at D_2 (geometric mean 11·2% (range

7·2–17·0%) *v* 11·4% (range 8·2–16·7%)), although in all cases glycaemic control tended to improve from D_1. Among patients with normal albumin excretion at D_1, those who progressed to microalbuminuria at D_2 did so with a significant worsening of the glycated haemoglobin value in the interim period compared with those remaining normoalbuminuric (geometric mean 13·8% (range 11·2–15·5%) *v* 10·8% (range 6·5–15·6%); p<0·05).

## Discussion

We report that, contrary to expectations, microalbuminuria (defined at 20–200 μg/min) among children and young adults with insulin dependent diabetes fails to progress consistently. This is in keeping with some recent reports in adults.[9][10] Overnight urine collections are thought to reduce the confounding effects that account for much of the intrapatient variation seen in albuminuria in diabetes.[11] However, even using this technique for urine collection in both studies, over half of the nine patients who initially had microalbuminuria had reverted to normal approximately three years later. In addition, contrary to other reports suggesting a progression of somewhere between 20 and 40% per year,[12][13] those remaining microalbuminuric did not appear to have progressed over this period. It could be argued that 20 μg/min is too low a cut off point for defining microalbuminuria. However, increasing the lower cut off to 30 μg/min,[2] identifying four patients at D_1, did not improve the predictability as two from the four completely reverted to normal at D_2. This finding could not be explained in terms of improved diabetes control. However, it is not surprising[14] that those patients with microalbuminuria at some stage during the study tended to have worse long term glycaemic control as reflected in higher values of glycated haemoglobin before the onset of the study.

Recently attention has been directed to so called 'borderline' microalbuminuria. Chase *et al* defined it as an albumin excretion level greater than upper 95th centile of normal (7·6 μg/min) but less than the lower limit of microalbuminuria (30 μg/min in their original work).[15] At D_1 we identified 11 patients with an AER greater than 8 but less than 20 μg/min. At D_2 six of these had reverted to normality, three remained in the borderline region, and two had progressed to microalbuminuria.

This study suggests that we may be wrong in extrapolating from studies conducted in adulthood, the natural history for microalbuminuria in childhood. Moreover, it has been shown that the predictive value for later overt nephropathy of microalbuminuria in patients with insulin dependent diabetes of long duration is poor.[9] In order to establish the significance of microalbuminuria in childhood a prospective, longitudinal study of incidence and progression is needed.
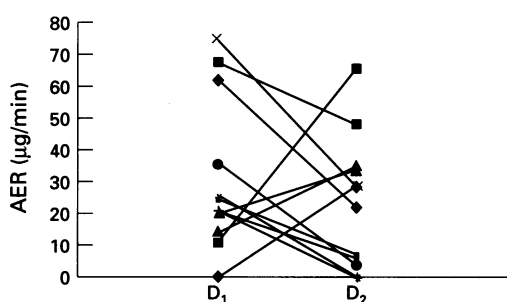
Graph showing the median AER in those with an abnormal level (lower limit 20 μg/min) at either D_1 or D_2 (or both). The 63 patients having normal excretion rates in both surveys are not shown.

Median AER at D_1 and D_2 in those with abnormal results at D_1; also included is an expected value for each patient in D_2 with microalbuminuria if the proposed progression rate was 36%/year

Case No	Duration of diabetes at D_1 (years)	Sex	Interval between D_1 and D_2 (years)	AER (μg/min) D_1	AER (μg/min) D_2	Projected AER at D_2 assuming progression at 36%/year
1	3·6	F	3·2	59	22	158
2	13·5	F	3·0	68	43	171
3	5·1	F	2·8	21	34	50
4	7·4	M	2·7	75	27	172
5	8·2	F	2·5	29	0	63
6	12·9	M	3·4	35	10	100
7	11·4	M	3·6	22	3	67
8	3·8	F	3·0	25	10	63
9	6·2	M	2·6	21	6	47

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